General

Guideline Title

Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Report of the Guideline Development Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Muayqil T, Gronseth G, Camicioli R. Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2012 Oct 2;79(14):1499-506. [34 references] PubMed

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Conclusion

For patients with suspected Creutzfeldt-Jakob disease (CJD), cerebrospinal fluid (CSF) 14-3-3 assays are probably moderately accurate in diagnosing CJD: sensitivity ~92%, specificity ~80% (multiple consistent Class II studies). Whereas a negative 14-3-3 assay may be helpful in reducing the suspicion of sCJD, a positive CSF 14-3-3 assay may be found in a potentially treatable case of dementia.

Recommendation

For patients who have rapidly progressive dementia and are strongly suspected of having CJD, and for whom diagnosis remains uncertain (pretest probability ~20%–90%), clinicians should order CSF 14-3-3 assays to reduce the uncertainty of the diagnosis (Level B).

Definitions:

Classification of Evidence for Diagnostic Accuracy

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable

reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion or a case report.

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is >2).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Sporadic Creutzfeldt-Jakob disease (sCJD)

Guideline Category

Diagnosis

Technology Assessment

Clinical Specialty

Internal Medicine

Neurology

Pathology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the available evidence for the diagnostic accuracy of cerebrospinal fluid (CSF) testing for protein 14-3-3 in patients with suspected sporadic Creutzfeldt-Jakob disease (sCJD)

Target Population

Patients who have rapidly progressive dementia and are strongly suspected of having Creutzfeldt-Jakob disease

Interventions and Practices Considered

Cerebrospinal fluid (CSF) testing for protein 14-3-3

Major Outcomes Considered

Sensitivity and specificity of diagnostic test

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2012 Guideline

The PubMed/Medline, Cochrane Library, and EMBASE databases were searched using the terms 14-3-3 protein, CSF analysis, Creutzfeldt-Jakob disease, prion disease, dementia, and rapidly progressive dementia (exploded terms where appropriate). The exact keyword search is available in appendix e-1 of the Data Supplement document (see the "Availability of Companion Documents" field). In addition, the reference lists of the articles identified were hand searched to identify articles that may have been missed in the initial search. Duplicates, reviews without original data, meeting abstracts, and case reports/series were excluded. The search included English-language articles and covered publications ranging from 1995 to January 1, 2011.

Studies in human subjects above 18 years of age were included. Non-sporadic cases from growth hormone use, genetic, iatrogenic (postsurgical), and new-variant (mad cow disease) prion diseases were excluded. Also excluded were non-Creutzfeldt-Jakob disease (CJD) prion disorders and animal studies. In studies that looked at a mix of sporadic Creutzfeldt-Jakob disease (sCJD) and other CJD subtypes, only the data on patients with sCJD were extracted for the analysis.

The search strategy identified 11,165 articles (3,488 from Medline, 5,254 from EMBASE, 59 from Cochrane Library, 2,364 from PubMed). After the primary screening in which the titles and abstracts were reviewed, 80 studies were deemed potentially relevant, and their full text was reviewed in the secondary screening process. Thirty-eight articles met inclusion criteria.

2015 Reaffirmation

MEDLINE was searched from January 2011 to July 2015 using the search terms 14-3-3 protein, CSF analysis, Creutzfeldt-Jakob disease, prion disease, dementia, and rapidly progressive dementia. Inclusion/exclusion criteria for the search included humans only, relevant to clinical questions; criteria used to screen search results were the same as described in the 2012 published guideline.

Number of Source Documents

38 articles met inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Diagnostic Accuracy

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion or a case report.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The articles were rated for their risk of bias according to the American Academy of Neurology classification of evidence criteria for diagnostic testing (see the "Rating Scheme for the Strength of the Evidence" field), and recommendations were linked to the level of evidence (see the "Rating Scheme for the Strength of the Recommendations" field). In accordance with these criteria, studies with incorporation bias (the results of the 14-3-3 protein assay influenced the determination of the presence of sporadic Creutzfeldt-Jakob disease [sCJD]) are rated Class IV, and studies with spectrum bias (which excluded a priori patients with uncertain diagnoses of sCJD) are rated Class III.

The number of patients, study design, data collection methods, patient population, diagnostic reference standard, and type of 14-3-3 assay used were collected. Other data extracted included the raw numbers of patients who tested positive vs. negative for cerebrospinal fluid (CSF) 14-3-3 and their clinical or pathologic diagnosis, or both.

Of the 38 articles included in the study, 9 were deemed Class II; no Class I studies were identified. The majority of the Class II studies were cohort studies with mixed retrospective and prospective data collection (table 1of the original guideline document). Fifteen studies were rated Class III, and another 14 were rated Class IV (table e-3 of the original guideline document). Downgrading was done if the cohort was incomplete. Spectrum bias in patients or controls was also a concern in a number of studies. All Class II studies enrolled patients with rapidly progressive dementia suspected of having Creutzfeldt-Jakob disease (CJD).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2012 Guideline

Recommendations are based on the strength of the evidence (see the "Rating Scheme for the Strength of the Recommendations" field). A pooled estimate of sensitivity and specificity was obtained for all studies rated Class II or higher.

2015 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) member who had expertise in neurologic disease conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields.

This guideline was approved by the Guideline Development Subcommittee on November 19, 2011; by the Practice Committee on February 17, 2012; and by the AAN Board of Directors on July 3, 2012.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Increased accuracy of diagnosis of sporadic Creutzfeldt-Jakob disease

Potential Harms

Potential false-positive and false-negative test results

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Muayqil T, Gronseth G, Camicioli R. Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2012 Oct 2;79(14):1499-506. [34 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Oct 2 (reaffirmed 2015 Jul 18)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

This guideline was developed with financial support from the American Academy of Neurology. None of the authors received reimbursement, honoraria, or stipends for their participation in development of this guideline.

Guideline Committee

Guideline Development Subcommittee of the American Academy of Neurology

Composition of Group That Authored the Guideline

Authors: Taim Muayqil, MBBS, FRCPC; Gary Gronseth, MD, FAAN; Richard Camicioli, MD, FRCPC

Financial Disclosures/Conflicts of Interest

Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of

the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects.

The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Disclosures

T. Muayqil reports no disclosures. G. Gronseth serves as an editorial advisory board member of *Neurology Now*, serves on a speakers' bureau for Boehringer Ingelheim, and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. R. Camicioli reports no disclosures. Go to Neurology.org for full disclosures.

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

Availability of Companion Documents

The following is available:

- Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Data supplement (e-appendices, e-tables). Available from the American Academy of Neurology (AAN) Web site.
- Diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2012. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.
- Diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Case presentation. St. Paul (MN): American Academy of Neurology. 2012. 6 p. Available in PDF from the AAN Web site.
- Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. Slide presentation. St. Paul (MN): American Academy of Neurology. 2012. Available from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site.

Patient Resources

The following is available:

- Diagnosing sporadic Creutzfeldt-Jakob disease: accuracy of the 14-3-3 protein test of the spinal fluid. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology. 2012. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.

NGC Status

This summary was completed by ECRI Institute on January 18, 2012. The currency of the guideline was reaffirmed by the developer in July 2015 and the summary was updated by ECRI Institute on January 18, 2017.

Copyright Statement

Disclaimer

NGC Disclaimer